APPENDIX I

Serial No.: 10/119,285

Docket No. 455-016 Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
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JEFFREY S. KIEL ET AL.	:	Examiner: SHEIKH, HUMERA N.
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Serial No.: 10/119,285	:	Group Art Unit: 1615
	:	
Filed: April 9, 2002	:	
	:	

For: PROCESS FOR PREPARING TANNATE LIQUID AND SEMI-SOLID DOSAGE FORMS

DECLARATION UNDER 37 CFR 1.132

1.) I am Jeffrey S. Kiel. I reside at 4253 Cherokee Trail, Gainesville, Georgia 30504. I am listed as a co-inventor in U.S. Patent Application serial no. 10/119,285.

2.) I graduated from the University of South Carolina in 1984 with a degree in PhD Chemistry. After graduation, I was employed by Bausch and Lomb as a Technical Section Manager from 1984 to 1988. Next, as a Laboratory Director at Applied Analytical Industries until 1991. I am now employed by Kiel Laboratories, Inc. as President. I have held that position for 13 years.

3.) I am listed as an inventor or co-inventor on a total of four U.S. Patents including 6,350,724, 6,214,381 and 5,902,595.

4. I have carefully reviewed and considered the specification of U.S. Patent Application serial no. 10/119,285, the Office Action of October 22, 2003 issued in that patent application and U.S. Patent 5,663,415 to Chopdekar et al. cited by the examiner in that Office Action to support the rejection of the claims presented in that patent application.

5.) The following information is provided in order to further illustrate the unique and non-obvious nature of the tannate salt conversion process employed by Kiel Laboratories which is the subject of U.S. patent application number 10/119,285. The information provided are mere examples of the superior results achieved by utilizing the Kiel process and should not in any way be construed as limitations of the Kiel method. The data presented in this declaration were collected in 2001 and 2002 as part of the normal course of business and were not originally collected for the purpose of supporting application number 10/119,285.

6.) One key difference between the method of the instant application and the prior art U.S. Patent 5,663,415 (the '415 patent) is the requirement for an additional isolation step during the production of tannate pharmaceutical products when using processes disclosed in that prior art patent. The ability to convert common pharmaceutical salts to the tannate salts directly within a pharmaceutically acceptable formulation process and the ability to process the tannate salts so formed into finished pharmaceutical products without additional isolation is an important advantage of the Kiel process claimed in the present application. The savings in time and material inherent in the Kiel process are very tangible although it is difficult to fully quantify them without being in possession of confidential information concerning the prior art processes. However,

objective measurements comparing the results of the Kiel process to that of the closest prior art are available.

7.) Table 1 provides a content variation comparison between active ingredient raw materials utilized during the manufacture of tannate pharmaceutical products using the prior art method of the '415 patent versus that utilized by the presently claimed Kiel method. The information concerning content variability in tannate salt raw materials was obtained from Cadilla Pharmaceuticals' published specifications and is typical of that in the art. The information concerning content variability in common salt raw materials, except for carbetapentane, was obtained from the USP, which is the source of industry accepted specifications. The specification for carbetapentane is an industry accepted value.

8.) Suppliers of common salt active ingredients must meet or exceed the USP specifications of content variability in order for them to be used in finished pharmaceutical products. Because there is no additional isolation step required after formation of the tannate salt during the Kiel process, essentially the entire amount of common salt active ingredient added to the formulation is processed directly into finished pharmaceutical product. Using prior art methods, the tannate salt of the active ingredient is first isolated, then processed into finished pharmaceutical product. The additional isolation step required by the prior art methods such as set forth in the '415 patent increases the content variability of the active ingredient material that is actually processed into finished pharmaceutical product. The data contained in Table 1 clearly illustrate this fact.

Table 1. **Comparison Between Raw Materials Added Directly to Pharmaceutical Products Prepared Utilizing the Prior Art Process Versus The Kiel Process**

Active Ingredient	Typical Supplier Specification for the Tannate Salt, Assay %*	Content Variation in Tannate Raw Material	Typical Supplier Specification for the Common Salt, Assay %†	Content Variation in Common Salt Raw Material	Decrease in Content Variation Using the Kiel Process
Chlorpheniramine	96%-104%	8%	98.0%-100.5%	2.50%	5.50%
Carbetapentane	96%-104%	8%	98.0%-100.5%	2.50%	5.50%
Pyrilamine	96%-104%	8%	98.0%-100.5%	2.50%	5.50%
Phenylephrine	96%-104%	8%	97.5%-102.5%	5.00%	3.00%

* Source: Cadilla Pharmaceuticals published specifications
† Source: USP published specifications which raw materials manufacturers must meet or exceed except for Carbetapentane, which is the industry accepted specification.

9.) The content variation range for the common salts of chlorpheniramine, carbetapentane, and pyrilamine is 2.50% whereas the content variation range for the tannate salts of each of these active ingredients is 8%. The content variation range for the common salt of phenylephrine is 5% whereas the content variation range for the tannate salt of phenylephrine is 8%. In each case, there is more variation in the active ingredient added to the formulation and processed directly into finished pharmaceutical product when prior art methods such as set forth in the '415 patent are utilized. The decrease in active ingredient variability inherent in the use of the presently claimed Kiel process is 5.50% for chlorpheniramine, carbetapentane, and pyrilamine, and is 3.00% for phenylephrine. In the manufacture of pharmaceutical products, these are very significant reductions in content variability.

10.) In order to achieve the same level of active ingredient content uniformity in the finished pharmaceutical product when using the prior art methods such as set forth in the '415 patent, a correction in the amount added to the formulation must be made each time a batch is prepared using a different lot of tannate salt raw material. In fact, this correction must be performed if the finished product is to meet current international pharmaceutical product standards of 95%-105% of the target active ingredient amount. Failure to do so may result in a sub potent and unmarketable product. The necessity of performing such a calculation decreases the efficiency of the manufacturing process and introduces another possible source of error.

11.) Tables 2 and 3 contain data collected during the manufacture of tannate pharmaceutical products using the presently claimed Kiel process. Table 2 contains data collected on mixing samples taken just after conversion to the tannate salt. Table 3 contains data collected on samples taken from bottles filled with finished pharmaceutical product produced using the presently claimed Kiel process. In each case, the data were collected as part of the manufacturing validation process. The lot numbers of the batches used to generate the data are shown in column 1. The active ingredients assayed are shown in column 2. The averages of the assays of each lot are shown in column 3. The range of each assay is shown in column 5, and the percent relative standard deviation, if determined, is shown in column 6. The bottom six rows of each table are a summary of the data collected including the number of lots of pharmaceutical product assayed to generate the data presented, the overall assay average, the range of the averages, and the % variability in content. In each and every case, the variability observed in the active ingredient content was much less than the typical 8% observed in tannate salt raw materials used in the prior art methods. The mixing data shows more variability in active

ingredient content than does the release data most likely due to incomplete mixing at the time of sampling.

Table 2. **Tannate Suspensions: Mixing Samples**

# of Lots	API's	OVERALL ASSAY AVERAGES	Avg. Range	Variation
6	Carbetapentane	99.4	97-101.7	4.70%
12	Chlorpheniramine	99.6	96-101.1	5.10%
9	Phenylephrine	103.9	100-106.2	6.20%
3	Pyrilamine	99.4	98.1-101.3	3.20%
3	Pseudoephedrine	99.4	97.7-102.5	4.80%

Table 3. **Tannate Suspensions: Release Samples**

# of Lots	API's	OVERALL ASSAY AVERAGES	Avg. Range	Variation
6	Carbetapentane	101.1	100.9-101	0.1%
12	Chlorpheniramine	99.4	98.2-100.1	1.9%
9	Phenylephrine	103.4	99.4-105.2	5.8%
3	Pyrilamine	101.2	99.7-104.1	4.5%
3	Pseudoephedrine	99.4	98.3-100.9	2.6 %

12.) The variability in content of phenylephrine active ingredient was larger than that of the other actives, and is illustrative of another important point. The increased variability in phenylephrine content of the mixing and release samples presented in tables 2 and 3 is a direct result of the increased variability in the content of phenylephrine raw material. The industry accepted content variability for phenylephrine raw material is

twice that for any of the other raw materials presented in Table 1 (5.00% versus 2.50%). Finished product cannot be produced with less variability than the starting materials used without carefully employing correction factors. The same principle applies globally to pharmaceutical products containing tannate salts of active ingredients. Those pharmaceutical products produced using methods which utilize isolated tannate salts of variable content as described in the '415 patent will inherently have more variation in the amount of active ingredient they contain than will those pharmaceutical products produced using the presently claimed Kiel method.

13.) The general cause of increased content variability inherently produced using the prior art methods is not difficult to explain. Each step or operation performed in a manufacturing environment introduces some level of variability into the finished product. When the operation in question involves isolating, purifying, or otherwise directly manipulating the amount of an active ingredient that is processed into a pharmaceutical product, the variability is focused on the amount of active ingredient contained in the finished pharmaceutical product. By eliminating the additional isolation step required by the prior art that is a potential source of increased content variability, the presently claimed Kiel process is able to produce a consistently better finished product.

14.) The decreased content variability that is a hallmark of the presently claimed Kiel process has many real world advantages. A better finished product in the pharmaceutical industry means a safer drug. The FDA as well as international pharmaceutical regulating entities views variations of only a few percent in the amount of active ingredient contained in a pharmaceutical product as potentially dangerous. Currently, however, the tannate drug products produced using the prior art '415 patent method and Kiel methods are not approved by the FDA under the modern Drug Price Competition and Patent Term

Restoration Act and are not subject to the same level of scrutiny that most new drug products face. This is because most drugs which are converted to tannate salts are actually older drugs that have been in the market place for many years in other forms such as the hydrochloride or bromide salt. These older drugs are converted to the tannate salt form in an effort to improve their therapeutic properties and continue their ability to be competitive in the market.

15.) The principle property affected by converting a drug to the tannate salt form is solubility, which normally decreases after conversion to a tannate from a hydrochloride or bromide salt. The decreased solubility attained in this manner gives the drug prolonged action characteristics. Changes in the content of tannate salt in a drug product can potentially alter the overall amount of drug taken as well as the rate the drug enters the body. Understandably then, increased variability in drug content leads to increased risk to the patient taking the drug product, which is the basis for tight regulation of drug content variability by the FDA and international agencies. The need for increased safety and content uniformity is multiplied by the fact that many of the tannate drug products are designed for use by children.

16.) It is understood that the FDA has plans to eventually force all older drug products to comply with the modern standards for safety and effectiveness. To accomplish this, the agency would have to remove each active ingredient or whole categories of active ingredients from the market until the manufacturer of such a product follows the current procedure for demonstrating safety and effectiveness. In order to demonstrate safety and effectiveness to the FDA, a very low variability in the amount of active ingredient placed into the drug product must be demonstrated by a manufacturer. Those drug products made using the presently claimed Kiel process will be in a better position to receive the

approval of the FDA than those made by other processes because or less content variability and less risk of dangerous interactions.

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

JEFFREY S. KIEL

3/30/04
DATE